^{111}Indium-diethylenetriaminepentaacetic acid-D-phenylalanine-octreotide
^{111}In-DTPA-OC

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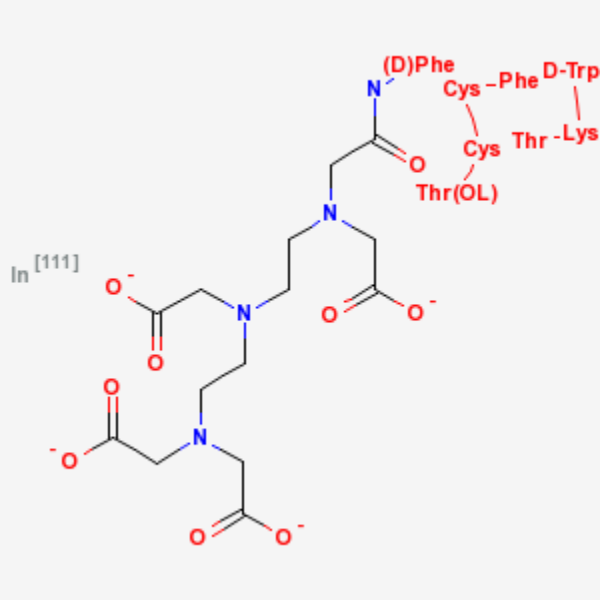
Chemical name: ^{111}Indium-diethylenetriaminepentaacetic acid-D-phenylalanine-octreotide
Abbreviated name: ^{111}In-DTPA-octreotide; ^{111}In-DTPA-OC; ^{111}In-DTPA-D-Phe-octreotide;^{111}In-pentetreotide
Synonym: OctreoScan® (commonly used brand name)
Backbone: Compound
Target: Somatostatin receptor (SSR)
Mechanism: Ligand binding to SSR subtypes 2 and 5; subtype 3 to a lesser degree
Method of detection: SPECT, scintigraphy (planar)
Source of signal: ^{111}In
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: Yes
Non-human primate studies: No
Human studies: Yes



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov/].

Background

[PubMed]

Somatostatin (SS) is a tetradecapeptide acting as an inhibitor of the release of somatotropin, glucagon, gastrointestinal hormones, and other secretory proteins. Critical to these actions is the expression of SS receptors (SSRs) present on cell membranes. Such receptors recognize and bind to the ligand with high affinity and specificity and generate a transmembrane signal that induces a biological response. SSRs have been found on a variety of neuroendocrine tumors and cells of the immune system, and five individual subtypes have been identified and subsequently cloned from animal and human tissues (1, 2).

^{111}In-DTPA-OC is a SSR analog that, over the last decade, has remained the most widely used radiopharmaceutical for the scintigraphic detection and staging of primary and metastatic neuroendocrine tumors bearing SSRs (mainly growth hormone-secreting pituitary tumors, endocrine pancreatic tumors, carcinoids, brain tumors, and other neuroendocrine tumors with typical amine precursor uptake and decarboxylation characteristics). It has also showed promising results in peptide-receptor radionuclide therapy (3-7). ^{111}In-DTPA-OC binds with high affinity to SSR subtypes 2 and 5 (sst_2 and sst_5) and to sst_3 to a lesser degree but does not bind to sst_1 and sst_4 (3, 8).

Synthesis

[PubMed]

^{111}In-DTPA-OC can be easily prepared from a commercially available kit (OctreoScan, Mallinckrodt Medical B.V., Petten, The Netherlands) consisting of two components to be mixed: 1) a sterile solution of 111 MBq/ml (3.0 mCi/ml) ^{111}In-choride in 0.02 N HCl with ferric chloride (3.5 µg/ml); and 2) a mixture of 10 µg of pentetreotide (DTPA-octreotide), 2.0 mg gentisic acid, 4.9 mg trisodium citrate, anhydrous, 0.37 mg citric acid, anhydrous, and 10.0 mg of inositol.

^{111}In-DTPA-OC can be synthesized and radiolabeled using the protocol described by Bakker et al. (9). One essential step of this method involves coupling DTPA to the protected OC in form of its anhydride (10). Radiolabeling of DTPA-OC with ^{111}In is done with a 40-70-molar excess of peptide over the radionuclide (2 µg of peptide in 20 µl of 0.1 M acetic acid with 37 MBq (1 mCi) of ^{111}In in 20 µl of 0.04 M HCl). The resulting specific radioactivity (radioactivity/mass labeled and unlabeled DTPA-OC) ranges from 17 to 25 MBq (0.46 to 0.67 mCi) (9).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro studies performed on SSR subtype 2 (sst_2)-positive rat pancreatic tumor cell lines CA20948 and AR42J and on the SSR-negative human anaplastic thyroid tumor cell line ARO showed that the internalization and the degradation of ^{111}In-DTPA-OC were receptor-specific, time- and temperature-dependent processes (11). The receptor-mediated internalization of ^{111}In-DTPA-OC results in the degradation to the final radiolabeled metabolite ^{111}In-DTPA-D-Phe. This metabolite is unable to pass through the lysosomal or other cell membrane(s) because of its polarity and, therefore, stays in the lysosomes, causing the long intracellular retention time of ^{111}In in sst_2-positive tumor cells.

The therapeutic effect of ^{111}In-DTPA-OC has been shown in several *in vitro* studies, such as the one by Duncan et al. (12) on sst_2-positive rat pancreatic tumor cell line CA20948.

Animal Studies

Rodents

[PubMed]

Only a limited number of animal models using human tumor tissue have been developed for experimental studies of radiolabeled OC. This is because human NE tumor cell lines expressing SSRs are uncommon. Pharmacokinetic and therapeutic studies have been performed essentially using rat exocrine pancreatic tumors (13, 14). A study by Adrian et al. (15) on nude mice carrying the human carcionoid GOT1 showed that the uptake in tumor and normal organs varied with the amount and administration mode of ^{111}In-DTPA-OC. Uptake was highest in tumor after 0.1 and 1 µg of ^{111}In-DTPA-OC and lowest in muscle, heart, and blood after 0.1 µg. The uptake decreased in lungs and spleen with higher amounts of ^{111}In-DTPA-OC, and in all organs studied, the tumor/normal tissue activity concentration ratio was maximal at 0.1 and 1 µg.

In separate *in vivo* studies on rats, Breeman et al. (16) and Kwekkeboom et al. (17) showed that the uptake of ^{111}In-DTPA-OC in receptor-positive tissues was not maximal at the lowest possible peptide amount or maximum-specific activity but was a bell-shaped function of the injected mass. Experimental data from rat studies by Slooter et al. (18) showed that high doses of ^{111}In-DTPA-OC could inhibit the growth of liver metastases after injection of sst_2 receptor-positive tumor cells in the portal vein, and that the number of SSR-positive liver metastases was significantly decreased after treatment with ^{111}In-DTPA-OC.

Other Non-Primate Mammals

[PubMed]

^{111}In-DTPA-OC scintigraphy was used to localize and stage spontaneously occurring insulinomas and gastrinomas in dogs (19, 20). In a study by Robben et al. (20), primary tumors and/or metastases of <3 mm in dogs could be visualized and localized by single photon emission computed tomography (SPECT) imaging. *In vitro* autoradiography and ligand binding studies showed that canine insulinomas expressed one subtype of SSR (sst_2). This is in contrast with findings in humans where, on the basis of ligand binding studies, different subtypes of SSRs have been identified.

SPECT imaging studies showed that in dogs, abdominal organ accumulation of ^{111}In-DTPA-OC primarily occurred in the kidneys, liver, gallbladder, gastric fundus, and intestines. This is very similar to what was reported in humans, except for the stomach, which shows no accumulation in human studies. Dog studies showed no splenic accumulation, and ^{111}In-DTPA-OC was primarily excreted via the kidneys (20, 21).

Non-Human Primates

[PubMed]

No reference currently available.

Human Studies

[PubMed]

In vivo human studies showed that ^{111}In-DTPA-OC was distributed to and localized in tumors within about 1 h of intravenous administration, and it was retained in the normal pituitary and thyroid glands, liver, spleen, urinary bladder, and to a lesser extent, in the bowel (22, 23). Hepatic and

biliary accumulations were found to be 2% of the administrated activity 4 h after injection. Organs showing the maximal retention were the spleen and kidneys, with estimated absorbed radiation doses of about 0.66 mGy/MBq (2.46 rad/mCi) and 0.49 mGy/MBq (1.80 rad/mCi), respectively. However, these estimated doses were found to be lower in the liver, spleen, and kidney, with patients bearing large tumors positive for SSRs (15).

The effective dose of ^{111}In-DTPA-OC for humans, based on data from the International Commission on radiological protection (ICRP) Publication 53 and reported in the OctreoScan kit, is 0.12 mSv/MBq (0.43 rem/mCi). Krenning et al. (21) reported a calculated effective dose equivalent of 0.08 mSv/MBq. Kwekkeboom et al. (17) reported a preferred dose of about 200 MBq (5.40 mCi), which makes it possible to perform SPECT and gives a better anatomic delineation than planar views.

It was shown that when a standard dose of 220 MBq (5.95 mCi) ^{111}In was coupled to <5 µg of DTPA-OC, the quality of scintigraphy was decreased, and the uptake in tumors was significantly reduced. ^{111}In-DTPA-OC scans should always be performed with at least 10 µg of peptide (as supplied in the OctreoScan kit formulation) (6).

Because of its relatively long effective half-life, ^{111}In-DTPA-OC may be used to see SSR-bearing tumors efficiently after 24 and 48 h, when interfering background radioactivity is minimized by renal clearance. Planar and SPECT studies should be performed preferably 24 h after injection. A higher lesion-detection rate of 24-h planar imaging over 4-h acquisition was reported by Jamar et al. (24).

Biodistribution studies by Forssell-Aronsson et al. (25) on tumors (breast and medullary thyroid carcinoma (MTC), differentiated thyroid tumors, endocrine pancreatic tumors (EPTs)) and normal tissues showed large inter- and intra-individual variations in ^{111}In activity concentration. This concentration was, in general, higher in carcinoids and some EPTs (range, 0.33-77% injected dose (ID)/kg) than in MTC and other tumors (0.017-7.8% ID/kg). Tumor/blood ratios >100 were found in most patients with carcinoids, EPTs, renal carcinoma, and neuroendocrine carcinoma (maximum value, 1500), whereas tumor/blood ratios were >80 in most other tumors. Normal tissue/blood ratios were in general ≤10, but higher values were found in liver, kidneys, and spleen.

Over recent years, various human studies aimed at investigating the potential ^{111}In-DTPA-OC in radionuclide therapy have been performed and reported in the literature (17, 26, 27).

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